Musculoskeletal steroid injection and concurrent influenza vaccination - analysis of current evidence, PCRMM.

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Abstract

Some clinicians are happy to deliver joint corticosteroid injections and influenza vaccination simultaneously. In contrast, others choose to postpone either procedure due to concerns that the corticosteroid injection may weaken vaccine effectiveness. Influenza causes significant morbidity and mortality (Lambert and Fauci, 2010). However, its prevalence can be reduced through yearly vaccination (Nichol *et al.,* 2007). Consequently, postponing the vaccination may risk influenza infection, especially if the patient fails to re-attend for vaccination.

The Advisory Committee members of Primary Care Rheumatology and Musculoskeletal Medicine Society wanted to demonstrate whether the corticosteroid dose used in musculoskeletal injections is enough to reduce the immune response to influenza vaccination to a clinically significant degree. The library service at East Lancashire Hospitals NHS Trust conducted a literature search to identify relevant evidence by using broad headings and search terms across EMBASE and MEDLINE. Over 500 studies were identified. Most analysed immunosuppressive drugs in addition to steroids. The author selected eight of the sourced studies which met the inclusion criteria for analysis. Six out of eight analysed studies, which met the inclusion criteria, indicated that systemic corticosteroids do not impact on immune responses to the influenza vaccination (De Roux *et al.,* 2006; Inoue *et al.,* 2013; Fairchok *et al.,* 1998; Kubiet *et al.,* 1996; Hanania *et al.,* 2004; Park *et al.,* 1996). One study was unable to provide a conclusion about corticosteroid therapy as combination of multiple immunosuppressive treatments were compared (Agarwal *et al.,* 2012). One study indicated increased relative risk (1.52) for influenza infection (Sytsma *et al.,* 2018), however due to poor study design no valuable conclusion could be drawn for clinical practice.

In a population of patients who receive the inactivated intramuscular influenza vaccination corticosteroid joint injections are not contraindicated with concurrent influenza vaccination. Joint injection therapy can be a good opportunity to deliver influenza vaccination or remind patients about benefits of the vaccination. Suggesting anything which may make an individual less likely to be vaccinated or to delay the vaccination is inappropriate as this could risk contracting influenza.

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The Primary Care Rheumatology and Musculoskeletal Medicine (PCRMM) Society gathers GPs and Allied Healthcare Practitioners with special interest in musculoskeletal (MSK) medicine. The following advice includes important information about the practice of MSK Corticosteroid (CS) injection during influenza vaccination season. Please note the full responsibility for the accuracy and information completeness about MSK injections and influenza vaccination given to patients rests on involved healthcare practitioners and their employers.

Introduction

Some clinicians deliver MSK CS injections alongside influenza vaccination during the same appointment. Others postpone either vaccination or MSK CS injection due to concern that CS injections can weaken the vaccine physiological response or increase the risk of contracting influenza. Moreover, many Patient General Directions (PGDs) advise against delivering both injections within a set time. Influenza can cause significant public health problem. Moreover, it can be fatal for some (Lambert and Fauci, 2010). However, with yearly vaccinations the prevalence and complications of this illness can be reduced (Nichol *et al.,* 2007). Therefore, the influenza vaccination helps keep populations safe. Consequently, postponing the vaccination may risk influenza infection, especially if patients fail to re-attend for the vaccination. The Advisory Committee members of PCRMM Society wanted to demonstrate whether the CS dose used in MSK injections is enough to reduce the immune response to influenza vaccination to a clinically significant degree.

Methods

The library service at East Lancashire Hospitals NHS Trust conducted a literature search to identify relevant evidence by using broad headings and search terms across EMBASE and MEDLINE. A secondary search identifying studies researching CS administration by whatever route and the effect on influenza vaccine response was subsequently completed due to a limited number of studies investigating only CS injection and influenza vaccination. The rational being that this information could then be applied from the analysis of the effects of systemic CS on vaccination effectiveness.

Over 500 studies were identified. Most analysed immunosuppressive drugs in addition to steroids. The author selected eight of the sourced studies which met the inclusion criteria for analysis. These studies generally concentrated on antibody production post influenza vaccination. By using the PICO framework, the search inclusion and exclusion criteria were facilitated (Methley *et al.,* 2014). The eight selected studies have been attached in Appendix of this document in Review of studies table (Table. 1). Since, this can facilitate reader's analysis of the individual studies' findings and level of scientific evidence.

Results

Six out of eight analysed studies, which met the inclusion criteria, indicated that systemic corticosteroids do not impact on immune responses to the influenza vaccination (De Roux *et al.,* 2006; Inoue *et al.,* 2013; Fairchok *et al.,* 1998; Kubiet *et al.,* 1996; Hanania *et al.,* 2004; Park *et al.,* 1996). One study was unable to provide a conclusion about CS therapy as combination multiple immunosuppressive treatments were compared (Agarwal *et al.,* 2012). One study indicated increased relative risk (1.52) for influenza infection (Sytsma *et al.,* 2018), however due to poor study design no valuable conclusion could be drawn for clinical practice.

Discussion

CS can treat many inflammatory and autoimmune conditions, with short and longstanding therapy prescribed depending on the indication (Kunisaki and Janoff, 2009). It is possible that CS can affect the human immunological system directly by affecting gene transcription or by wider influence of lymphoid and non-lymphoid cells (Boupas *et al*., 1993). Since MSK CS injections can potentially create a transient suppression of endogenous cortisone production, an immunosuppressive effect may occur (Habib *et al.,* 2014; Cain and Cidlowski, 2017). Unfortunately, high-quality data about the risk of MSK CS injections and susceptibility to influenza or effect on influenza vaccination is lacking, despite years of CS use to treat arthritis (Hollander *et al.,* 1951). Undoubtedly, there are many factors which can influence the vaccine response including age of patient, previous vaccinations or infections and obesity (Weinberger *et al.*, 2020; Szilagyi *et al.,* 1992; Mauch *et al.,* 1995). Therefore, addressing those factors where possible would be beneficial for vaccinated populations.

The immune system fights influenza infection through humoral and cellular mechanisms and a specific T-lymphocyte dependent antibody is produced to provide protection to influenza virus (Grant *et al.,* 2014). Most analysed studies concentrated on physiological response to the vaccination

by antibody production. Although, the interpretation of such studies can be challenging. Firstly, as influenza vaccine contains antigens of a few virus strains changing on yearly basis, a patient vaccinated against the same strain from previous years might respond differently from a vaccine naïve patient. Moreover, the unpredictable yearly variation of the circulating virus can cause infection by a virus not present in the vaccine, which could be inappropriately classed as a vaccination failure (Kunisaki and Janoff, 2009). Lastly, studies assessing vaccination effectiveness in patients using multiple immunosuppressive drugs at once makes drawing conclusions about one particular drug difficult. Nevertheless, six out of eight analysed studies indicated that systemic CS do not influence the physiological antibody response towards influenza vaccination. The most frequent reason expressed by some clinicians regarding the potential adverse effect of MSK CS injection on response to influenza vaccination relates to possible systemic effect of CS following the injection. However, analysis of this evidence suggests that MSK CS injections do not adversely affect concurrent influenza vaccination, since systemic treatment with CS in the analysed studies did not compromise physiological response to influenza vaccine.

There are several aspects to the question of steroid use and vaccinations that can be clarified by The Green Book (PHE, 2019). Currently, this is the leading UK resource providing information about vaccination and immunisation. As the influenza vaccine delivered by parenteral route is a not live virus, it can be given to patients with concurrent high-dose glucocorticoids administration regardless of immune status (Fairchok *et al.,* 1998, PHE, 2019). Currently, in the UK there is only one live attenuated influenza vaccine, the rest are inactivated. The live influenza vaccine is administered to children aged between 2 to 18 years old by nasal spray, the inactive influenza vaccines are delivered by intramuscular injection. Moreover, the live influenza vaccine is not contraindicated for patients on low dose systemic CS (PHE, 2019).

Conclusion

Analysis of this research demonstrates a lack of strong evidence that concurrent MSK CS injections can alter the physiological response to vaccine against influenza. In a population of adults and children who receive the inactivated intramuscular influenza vaccination MSK CS injections are not contraindicated with concurrent influenza vaccination regardless of immune status. MSK injection therapy practice can be a good opportunity to deliver influenza vaccination as well as a CS injection or remind patients about benefits of the vaccination. It should be emphasised that the influenza vaccination is effective, saves lives and reduces NHS costs. Suggesting any policy which may make an individual less likely to be vaccinated or risks delaying vaccination should therefore be avoided.

References

- Agarwal, N., Ollington, K., Kaneshiro, M., Frenck, R., Melmed, GY., (2012) "Are immunosuppressive medications associated with decreased responses to routine immunizations? A systematic review." in *Vaccine*, 30(8), pp. 1413-1424.
- Boumpas, DT., Chrousos, GP., Wilder, RL., Cupps, TR., Balow, JE., (1993) "Glucocorticoid therapy for immunemediated diseases: basic and clinical correlates." Annals of Internal Medicine, 119(1), pp. 198–208.
- Cain, DW., Cidlowski, JA., (2017) "Immune regulation by glucocorticoids" *in Nature Reviews Immunology,* 17(4), pp. 233-247.
- De Roux, A., Marx, A., Burkhardt, O., Schweiger, B., Borkowski, A., Banzhoff, A., Pletz, M., Hartmut, L., (2006), "Impact of corticosteroids on the immune response to a MF59-adjuvanted influenza vaccine in elderly COPD-patients." in *Vaccine*. 24, pp. 1537-1542.
- Fairchok, MP., Trementozzi, DP., Carter, PS., Regnery, HL., Carter, ER., (1998) "Effect of Prednisone on Response to Influenza Virus Vaccine in Asthmatic Children." *Archives of pediatrics and adolescent medicine,* 152(12), pp. 1191–1195.
- Grant, EJ., Chen, L., Quiñones-Parra, S., Pang, K., Kedzierska, K., Chen, W., (2014) "T-cell immunity to influenza A viruses" in *Critical Reviews in Immunology*, 34(1), pp. 15-39.
- Habib, G., Jabbour, A., Artul, S., Hakim, G., (2014) "Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: a randomized controlled study" *in Clinical Rheumatology*, 33(1), pp. 99-103.
- Hanania, NA., Sockrider, M., Castro, M., Holbrook, JT., Tonascia, J., Wise R, Atmar, RL., (2004) "Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy." in *The Journal of Allergy and Clinical Immunology*, 113, pp. 717–24.
- Hollander, JL., Brown, EM., Jr., Jessar, RA., Brown, CY., (1951) "Hydrocortisone and cortisone injected into arthritic joints: comparative effects of and use of hydrocortisone as a local antiarthritic agent." *in The Journal of the American Medical Association*, 147(17), pp. 1629-1635.
- Inoue, S., Shibata, Y., Takabatake, N., Igarashi, A., Abe, S., & Kubota, I. (2013). "Influence of corticosteroid therapy on the serum antibody response to influenza vaccine in elderly patients with chronic pulmonary diseases." in *EXCLI journal*, 12, pp. 760–765.
- Kubiet, MA., Gonzalez-Rothi, RJ., Cottey, R., Bender, BS., (1996), "Serum antibody response to influenza vaccine in pulmonary patients receiving corticosteroids." in *Chest*, 110(2), pp. 367-370.

- Kunisaki, K. M., Janoff, E. N., (2009), "Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses." in *The Lancet. Infectious diseases*, 9(8), pp. 493–504.
- Lambert, CL., Fauci, AS., (2010) "Influenza vaccines for the future" in *The New England Journal of Medicine*, 363, pp. 2036-2044.
- Mauch, J., Crouch, NA., Freese, DK., Braunlin, EA., Dunn, DL., Kashtan, CE., (1995) "Antibody response of pediatric solid organ transplant recipients to immunization against influenza virus" *in The Journal of Pediatrics*, 127, pp. 957- 960.
- Methley, A. M., Campbell, S., Chew-Graham, C., McNally, R., Cheraghi-Sohi, S. (2014) "PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews" in *BMC health services research*, *14*(579).
- Nichol, KL., Nordin, JD., Nelson, DB., Mullooly JP, Hak, E., (2007) "Effectiveness of influenza vaccine in the community-dwelling elderly" in *The New England Journal of Medicine*, 357, pp. 1373-1381.
- Park, CL., Frank, AL., Sullivan, M., Jindal, P., Baxter, BD., (1996) "Influenza vaccination of children during acute asthma exacerbation and concurrent prednisone therapy." in *Pediatrics,* 98, pp. 196- 200.
- PHE (2019), *The Green Book*. Available at: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book#the-green-book , (Accessed: 09/08/2020).
- Sytsma, TT., Greenlund, LK., Greenlund, LS., (2018), "Joint corticosteroid injection associated with increased influenza risk." in *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*, 2, pp. 194–198.
- Szilagyi, PG., Rodewald, LE., Savageau, J., Yoos, L., Doane, C., (1992) "Improving influenza vaccination rates in children with asthma: a test of a computerized reminder system and an analysis of factors predicting vaccine compliance" in *Pediatrics*, 90, pp. 871- 875.
- Weinberger, B., (ed) (2020), "Vaccines for Older Adults: Current Practices and Future Opportunities." In *Interdisciplinary Topics in Gerontology and Geriatrics,* 43, pp. 86–97.

Appendix.

Table 1. Review of studies table

Author/ Date	Journal	P	I	C	O	Comments
De Roux et al., 2006	*Vaccine*	174 PT enrolled and 162 completed the study 88 M and 74 F. Mean age was 71.3 YO with COPD	IG: (a) >10 mg of prednisolone/day (SS) max of 30mg 2/52 prior and 3/52 after Vac 40 PT; (b) inhaled steroids (IS) 90 PT; Both groups were given influenza Vac.	CG: (c) no CS treatment 44 PT Given influenza Vac.	Comparison: level of Influenza Antb checked initially and 4/52 and 24/52 post vaccination. Systemic CS did not affect body response to vaccination	Study type: Case Controlled Low number of participants Good selection of study sample ruling out other comorbidities Level of evidence: 4
Sytsma *et al.,* 2018	*Mayo Clinic Proceedings: Innovations, Quality & Outcomes*	58,304 PT during the influenza seasons between 08/2012, and 03/2017 from	IG: 4804 PT had a large MSK CS injection Given influenza Vac during the influenza seasons	CG: 43,236 PT 50 YO or more Given influenza Vac during the influenza seasons	Comparison: IG PT had increased risk for influenza infection (relative risk, 1.52; 95% CI, 1.20-1.93) in comparison to CG. F less than 65 YO had the highest risk.	Study type: retrospective cohort study The overall percent of PT with RA statistically higher in IG 4.27% in comparison to CG 1.29%. RA PT potentially received immunosuppressants which could affect the outcome. Mean CS dose 65.9 mg (range 40-120 mg) 59.5% PT received 80mg steroids or more 36.7% had multiple CS injections at one visit CS received: Methylprednisolone acetate 78.9%, Betamethasone 10.9%, Triamcinolone acetonide 10.1% Relatively large doses of CS used, multiple and major joint injections sites in one sitting which poorly represents MSK practice in the UK The diagnosis of influenza based only on clinical findings recorded in the notes. Therefore, the true diagnosis of influenza cannot be made. The patients did not receive viral swab tests to confirm influenza diagnosis. We do not know if the PT diagnosed as having influenza had indeed the type of influenza to which have been Vac for in the given year. Perhaps a virus of influenza gave the symptoms to which PT did not receive Vac. Unable to assess of the timing of the injection and vaccination. Level of evidence: 4

Author/ Date	Journal	P	I	C	O	Comments
Inoue *et al.,* 2013	EXCLI Journal	48 elderly PT with COPD who received influenza Vac.	IG: a.) oral CS therapy group Mean CS dose: equivalent to 10.0 mg/day of prednisolone (4 M, 7 F; mean age, 66.1 ± 10.6), b.) inhaled CS therapy group (8 M, 9 F; mean age, 62.4 ± 16.0).	CG: c.) no CS therapy (17 M, 3 F; mean age, 72.3 ± 7.9),	Long-term CS oral/inhaled treatment did not affect the immune response to the influenza Vac.	Study type: prospective cohort study Study limitations: • Performed at a single centre, and small number of PT. • Relatively low dose of systemic CS therefore, unable to assess the effects of high dose of CS • Most PT had influenza Vac in the past therefore, this may have influenced the outcomes. Level of evidence: 4
Faircho k *et al.,* 1998	Archives of pediatri cs & adolesc ent medicin e	Children 6/12 to 18 YO receiving influenza Vac 58 PT enrolled and 50 PT completed the study.	IG: 21 children receiving Prednisone for acute exacerbatio n of asthma (2 mg/kg per day fro 5 days)	CG: 37 children using preventativ e dose of inhaled CS	CS bursts did not lower the response to influenza Vac	Study type: Prospective cohort study Good patient selection and exclusion criteria Study Limitations: Performed at a single centre, and small number of PT. Level of evidence: 4
Agarwal *et al.,* 2012	Vaccine	Systematic review of studies papers evaluating response to various vaccines in Pt on immunosup pressants			15/972 papers met inclusion criteria. 10 papers evaluated responses to influenza vaccine. 5/10 of those papers showed partially reduced response to vaccine PT using more than one immunosuppressive drug at the same time were less likely to respond to VAC.	Study type: Systematic review This systematic review included PT with various illness. Including post-transplant PT and autoimmune conditions. The analysed treatment regimens were heterogenic. Therefore, no conclusion can be made regarding outcomes of using specific drugs. Level of evidence: 1

Author/ Date	Journal	P	I	C	O	Comments
Kubiet *et al.,* 1996	Chest	39 PT with pulmonary conditions Who received influenza Vac	IG: 25 PT receiving CS (prednisone equivalent) 2.5 to 60 mg/day (mean±SD= 17±15 mg) for a month prior the Vac	CG: 14 PT not receiving CS	PT receiving CS can generate an adequate Antb response. Long-term CS therapy should not prevent receiving the influenza Vac	Study type: Prospective cohort study Small number of participants PT were exposed to influenza Vac in previous years which could affect the outcome Level of evidence: 4
Hanania et al., 2004	Journal of Allergy Clinical Immunology	294 PT 3-64 YO with asthma Received either of placebo or influenza Vac	IG: group 1 (148 PT) on medium and high of inhaled oral	CG: group 2 (146 PT) were not on CS or on low dose	Serologic responses to each influenza Vac antigen were significantly higher in Vac PT than in placebo group The immune response to the influenza A antigens is not negatively influenced by CS therapy High-dose Inhaled CS may lower the response to influenza B antigen, but this needs further studies to assess this observation	Study type: prospective randomized, double-masked, placebo-controlled, crossover 6 PT (4 Vac, 2 placebo group) were on reported chronic doses of oral CS. The mean daily dose pf 26.7 mg prednisolone equivalent. Therefore, no conclusions can be found about chronic oral CS therapy. Level of evidence: 2
Park *et al.,* 1996	Pediatrics	109 PT children aged 6/52-18 YO with asthma Who received influenza Vac	IG: 50 PT with acute exacerbation of asthma treating with prednisone	CG: 59 PT without asthma symptoms (no prednisone, treatment)	Antb responses to influenza Vac were not different in both groups.	Study type: Study type: Prospective cohort study Small sample Only Abstract accessed Unknown dose of prednisolone Unable to assess full study methodology Level of evidence: 4

P (Population): children and adults receiving Influenza vaccine, I (Intervention): steroid injection for MSK problem or systemic steroid use, C (Comparison): effectiveness of flu vaccination, O (Outcome): Antibodies level comparison, Confirmed Influenza infection

IG: Intervention Group, CG: Control Group, CS: Corticosteroid, Vac: Vaccination/Vaccinated, M: Male, F: Female, Antb: Antibody/Antibodies, PT: Patient/Patients, RA: Rheumatoid Arthritis, COPD: Chronic Obstructive Pulmonary Disease, MSK: Musculoskeletal, YO: Years Old,